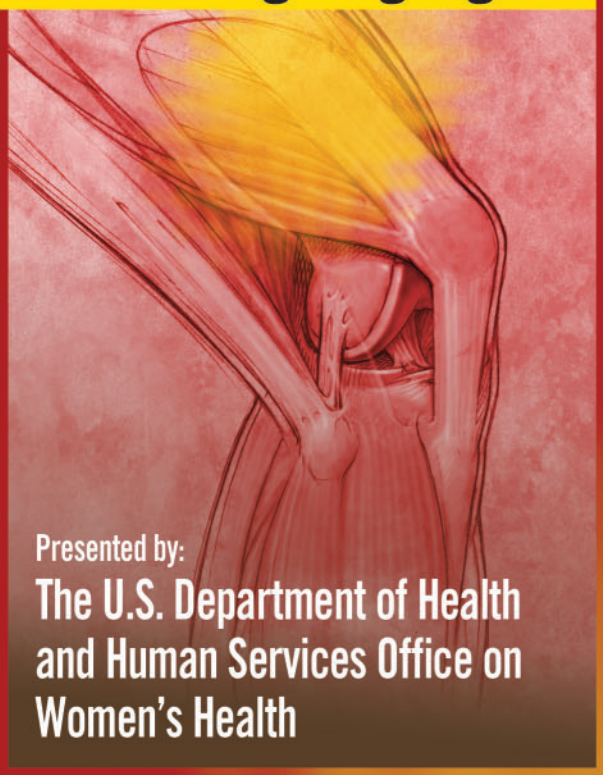
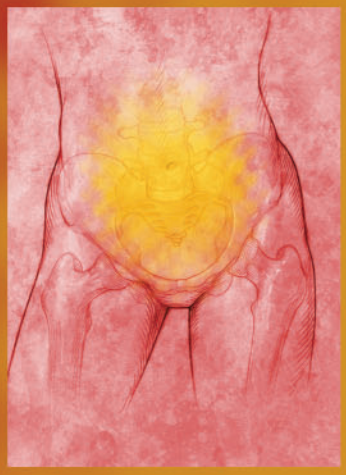
Proceedings Highlights

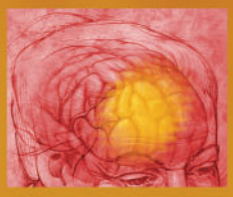


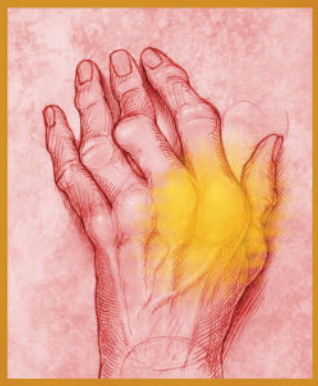
State-of-the-Art Management of Mild-to-Moderate Pain

From Adolescence Through Old Age

Presented by:
The U.S. Department of Health and Human Services Office on Women's Health







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STATE-OF-THE-ART MANAGEMENT OF MILD-TO-MODERATE PAIN FROM ADOLESCENCE THROUGH OLD AGE PROCEEDINGS HIGHLIGHTS

OVERVIEW

Pain, highly prevalent in the general population, is associated with serious physical, psychological, and socioeconomic consequences that can delay recovery, diminish quality of life, and increase utilization of healthcare resources. Emerging data suggest that the costs to individuals and society are underestimated and present a significant economic burden.

Historically, pain has been managed inadequately, in part because it was conceptualized as a normal consequence of illness, aging, and daily life. Within this context, patients often failed to seek medical attention for their pain. In addition, concern about addiction and adverse events associated with pain medications has contributed to insufficient management.[1] The emergence of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for pain management, which took effect in January, 2001, marked a paradigm shift from the "mystique of pain" to pain as the "fifth vital sign" that can be assessed and controlled in an evidence-based framework.[2,3] In parallel, expanding knowledge about biology and pathophysiology of pain and its manifestations has contributed to improvements in treatment.

LEARNING OBJECTIVES

After reading this newsletter, the healthcare professional should be able to:

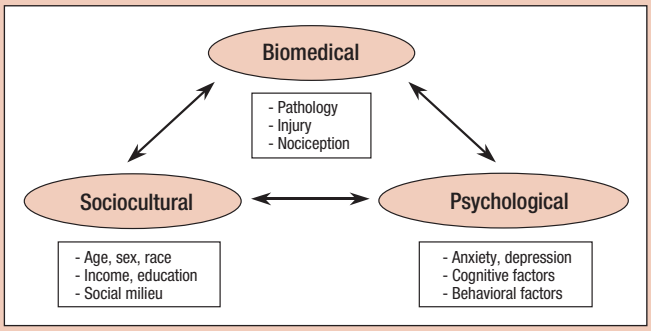
- Educate patients on the safe use of pain medications
- Identify and treat mild-to-moderate pain appropriately
- Explain the impact that gender differences may play on pain perception and perceived effectiveness of therapy
- Explain the role of age and cognitive function on the perception of pain, ability to communicate with caregivers, and on perceived effectiveness of therapy
- Evaluate psychosocial, socioeconomic, quality of life, and pharmacoeconomic issues related to mild-to-moderate pain and pain management
- Consider the influence of pain on healthcare professional–patient interactions
- Explore issues related to common medical conditions that cause pain
- Examine the risks and benefits of commonly used analgesics in the management of mild-to-moderate pain
- Discuss a practical and rational approach for primary care providers to manage mild-to-moderate pain

INTENDED AUDIENCE

Primary care physicians

FIGURE 1

A biopsychosocial model of pain



Recently, a group of experts in various aspects of pain management met under the auspices of the United States Department of Health and Human Services Office on Women's Health to examine the impact of mild-to-moderate pain on individuals, society, and the healthcare system and to present and discuss information for educational initiatives designed to help improve clinical outcomes. The focus of these deliberations was mild-to-moderate pain—a score of 2 to 6 on a visual analog or numeric rating scale; 0 represents no pain and 10 represents severe pain.[4] This issue of *Clinical Courier®* presents highlights of the roundtable proceedings.

Pain: A Multidimensional Experience

The International Association for the Study of Pain® (IASP®) defines pain as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*"[5]

Broadly, pain comprises 2 classes—nociceptive and neuropathic pain. Nociceptive pain results from stimulation of nociceptive receptors transmitted over intact neural pathways. This is what we think of as "normal" pain occurring in response to a potentially damaging stimulus. In contrast, neuropathic pain results from damage to neural structures and may often involve neural supersensitivity, exemplified by phantom limb pain.

Pain definitions accommodate a vast number of etiologic factors, which may be subsumed in a multidimensional model composed of biomedical, sociocultural, and psychological considerations (Figure 1). The validity of this interactive model is supported by both animal and human studies demonstrating effects of gender, age, ethnicity, and psychological, cognitive, and cultural factors in nociception as well as in drug responsivity.[6-13]

For example, male rats demonstrate a higher pain threshold to mechanical nociception than do females and have greater responsivity to μ-opioid agonists.[6] Human females consistently have lower pain thresholds than males and account for a higher proportion of those with chronic pain conditions. The causal basis of the observed differences is unknown, but experimental data provide some interesting clues. For example, painful laser stimulation resulted in different cerebral activation patterns in human males and females. Investigators speculated that these differences in pain processing may be important in the various clinical conditions in which prevalence is higher in females, such as migraine.[7] In another study, gender differences in the use of prescription pain medications emerged at puberty and continued into adulthood.[14] Although hormonal/development factors could account for these differences, puberty also marks a time of expanding differences in culturally influenced sex roles. In an experiment using electrical pain, men exhibited greater responsivity to ibuprofen than women, although gender differences in analgesia with ibuprofen were not observed after dental surgery.[15,16] Numerous other examples of gender differences have been described, suggesting that additional study is needed to clarify potentially important clinical implications of these differences.

Ethnic differences in pain severity, disability, and connotation have been reported in a number of circumstances. Generally, whites report less pain and fewer pain consequences than blacks and Hispanics.[17,18] The reasons for these differences are unknown, but it is likely that cultural factors contribute substantially to the interpretation of pain. Of more immediate concern are findings that minorities may be undertreated for pain.[19-25]

State-of-the-Art Management of Mild-to-Moderate Pain From Adolescence Through Old Age is a certified continuing education activity providing an in-depth, expert review and analysis of recent scientific advances and clinical controversies in the management of mild-to-moderate pain. The views presented are those of the faculty and/or contributing editors and not necessarily those of the producer, commercial supporter, the US Department of Health and Human Services Office on Women's Health, or the University of Colorado School of Medicine. Some information presented in this newsletter may be off label. Before using any product discussed in this publication, clinicians should consult the full prescribing information.

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State-of-the-Art Management of Mild-to-Moderate Pain From Adolescence Through Old Age, reports highlights from a roundtable presented by the US Department of Health and Human Services Office on Women's Health, under the auspices of the University of Colorado School of Medicine, and in cooperation with the American Pharmacists Association, the American Geriatrics Society and the American Academy of Nurse Practitioners.

This material is based upon a review of multiple sources of information, but is not exhaustive of the subject matter. Healthcare professionals and other individuals should review and consider other publications and materials about the subject and not rely solely upon the information contained within this publication.

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TABLE 1

Estimated Prevalence of Common Pain Conditions in the United States

Condition	Prevalence
Arthritis	
Osteoarthritis	• 20 million individuals in 2000; projected to double by 2020[158]
Female/male	• 20% vs 15%[159]
Backache	• 15% to 20%[107] • 26 million between the ages of 20 and 64[160] • 67% lifetime prevalence[160]
Female/male	• 1.2:1 ratio[97]
Headache	• 93% of population annually (95% women, 90% men)[161]
Migraine	• >28 million[162]
Female/male	• 18.2% vs 6.5%[162]
Dysmenorrhea*	• Up to 90% of women[163] • 72% in a prospective study[164]

*The prevalence estimates for dysmenorrhea vary widely, depend on a number of variables, and have been reviewed in detail.[165]

Finally, psychological and cognitive factors can modulate pain perception. Stress effects, for example, depend on the type and duration of the stressful stimuli. Experiments in animals and humans suggest that stress has bidirectional effects. Fear tends to inhibit pain and anxiety enhances it.[26, 27] Various forms of psychological distress and cognitive expectations can increase the risk of chronic pain, the amount of analgesic used, and the level of pain severity.[10,26,28-36]

THE EPIDEMIOLOGY OF PAIN CONDITIONS

Pain is ubiquitous (Table 1), and recent survey data confirm that it is undertreated. According to a Gallup survey, approximately 42% of adults in the United States suffer daily pain, and 89% have pain at least once a month.[37] In the over 65 population, 55% have daily pain and 88% cite aging as the cause of their pain.[37] Over 50 million Americans suffer from chronic pain such as joint pain, low back pain, and headache, and nearly 25 million experience acute pain each year due to injuries or surgery.[38] Importantly, 64% of respondents in the survey would see a physician about their pain only when it becomes intolerable. Only 42% of those who see a physician about pain believe that their physicians understand their pain.[37] In many of these conditions, women suffer more frequent pain and believe they have less control over their pain than do men (39% and 48%, respectively).[38] The prevalence of migraine in women is approximately 3 times that of men, and substantially more women have osteoarthritis (OA) and back pain than do men. Taken together, these pain conditions represent a significant public health issue.

CONSEQUENCES OF CHRONIC PAIN

Uncontrolled pain results in substantial socioeconomic burdens. A major contributor to the costs is the utilization of healthcare resources. A 1996 survey showed that patients with musculoskeletal conditions were 50% more likely to utilize healthcare services than those without chronic conditions.[39] The largest components of care were hospitalization (37%), physician visits (23%), and prescription drugs (16%).[39] Other studies have shown that approximately one third of medical expenditures for arthritis can be attributed to adverse gastrointestinal (GI) effects of therapy.[40,41]

Overall, billions of dollars are expended on therapies,[40] some of which may not be cost-effective because of treatment-related complications and adverse events. More than 30 million people take a nonsteroidal anti-inflammatory drug (NSAID) daily, and GI complications related to NSAID therapy are the most prevalent category of adverse drug reactions.[42] For example, the annual relative risk (RR) of GI complications in users of NSAIDs compared to nonusers is approximately 4.2.[42] An estimated 103,000 hospitalizations for severe, NSAID-related, GI complications are associated with annual direct costs in excess of $1 billion.[43] Finally, 16,500 deaths per year are attributable to GI complications of NSAIDs in patients with rheumatoid arthritis or OA.[42] Chronic pain costs employers in the United States an estimated $60 billion annually in lost productivity.[44]

Other consequences of chronic pain may be more difficult to measure, for example potential alterations in the physician-patient interaction. In a recent study, 509 patients were assigned to visit primary care physicians (PCPs), and physician practice styles were assessed by videotape. When patients were in pain, physicians spent less time on preventive services and in encouraging active participation in care. More time was spent on history taking and the physical examination.[45] Reductions in communication time may have a deleterious effect on clinical outcome.

MANAGING MILD-TO-MODERATE PAIN

Interventions for pain management span an array of modalities including psychosocial, pharmacologic, and physical—the treatment triad (Figure 2). A key challenge is to integrate and incorporate these options into clinical practice.

Nonpharmacologic Approaches

Interventions include patient education, distractions, relaxation/biofeedback, cognitive therapy, and hypnosis.[46] The Arthritis Self-Management Program (ASMP), based on the concept of self-efficacy, is a model for the management of mild-to-moderate pain. Albert Bandura defines self-efficacy as "*people's beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives. Self-efficacy beliefs determine how people feel, think, motivate themselves and behave.*"[47] In clinical trials, the ASMP has been shown to reduce pain significantly at 4 months, with the improvement being maintained at a 20-month follow-up assessment.[48,49] More specific information about the ASMP can be found at http://patienteducation.stanford.edu/.

The effectiveness of psychological interventions for pain management has been well documented. A National Institutes of Health Technology Assessment Panel determined that strong evidence supports the use of relaxation techniques in reducing chronic pain, strong-to-moderate evidence supports hypnosis, and moderate evidence supports cognitive behavioral treatments and biofeedback.[50] For example, preoperative coping imagery reduces pain and cortisol responses following abdominal surgery, while hypnosis and relaxation training can reduce experimental and acute clinical pain.[51-54]

FIGURE 2

The treatment triad

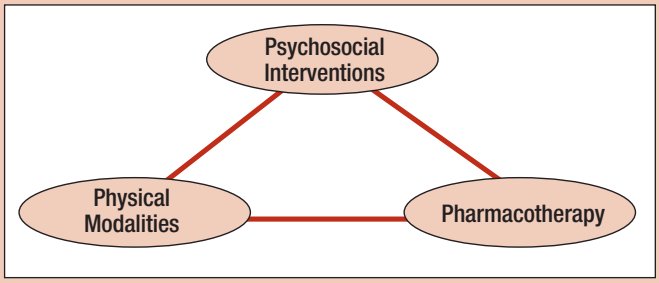
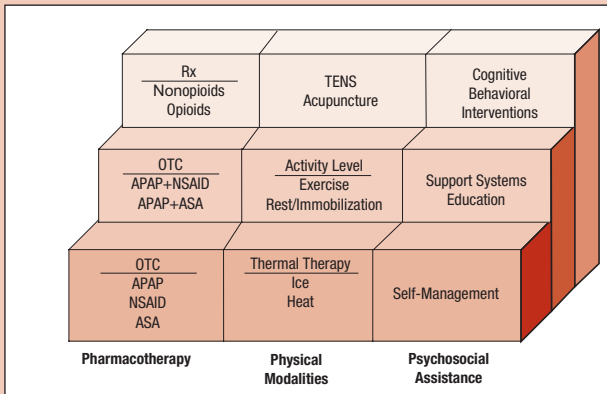


FIGURE 3

A stepwise approach to management of mild-to-moderate pain



Rx, prescription; TENS, transcutaneous electrical nerve stimulation; OTC, over-the-counter; APAP, acetaminophen; NSAID, nonsteroidal anti-inflammatory drug; ASA, aspirin.

Physical Modalities

Thermal and physical therapy (PT), acupuncture, weight loss, and transcutaneous electrical nerve stimulation (TENS) each have potential roles in the management of mild-to-moderate pain. The evidence basis is limited for some of these methods, but in general the concept of multimodal therapy is well supported.[55-59] One means of integrating multimodal therapy into practice is suggested in the stepwise approach illustrated in Figure 3. Ongoing research should continue to shed light on the efficacy, safety, and role of each of these modalities in pain management.

Nonprescription Pharmacotherapy

The large variety of analgesic brands, formulations, and dosages provide consumers with many therapeutic choices targeting their specific symptoms. Despite the numerous products on pharmacy shelves in the United States, there are only 5 active analgesic ingredients: acetaminophen, aspirin, ibuprofen, ketoprofen, and naproxen sodium. These agents play an important role in pain management, but appropriate use can be improved. Consumers often neglect to read product labels and can be poorly informed about safe dosing and administration. When consumers fail to read the labels, they unwittingly put themselves at risk of overmedicating, with its attendant adverse consequences. Five distinct therapeutic entities, as well as combination products, are available for oral, nonprescription analgesia. Specific counseling considerations apply to each entity (Table 2, page 4).

Generally, consumers need to be educated or reminded that nonprescription status does not confer unqualified safety. Over-the-counter (OTC) products, like prescription medications, can be potentially harmful if not taken as directed. Effective and safe use of these products can be improved when consumers are advised on when and how to use them and are encouraged to read labels carefully, to start with single agents, to avoid duplication of ingredients, and to understand when to alert physicians about any adverse effects that occur. Patients should be urged to consult physicians if fever lasts more than 3 days in adults and children, and if pain lasts 10 days or more in adults and 3 days or more in children.

TABLE 2

Nonprescription Analgesic Agents for Oral Use

Categories/Products	Products	Key Counseling/Usage Issues*
Acetaminophen • Analgesic • Antipyretic		• Can be used in patients with GI distress, peptic ulcer disease, asthma, gout, allergy, or sensitivity to aspirin, and in children • Does not have anti-inflammatory effects • Consumers should review the labels of all the medications they are taking as acetaminophen is common amongst various preparations • Consumers should be aware that dosing varies depending on dosage form • Patients who consume 3 or more alcoholic drinks daily should consult their physician
NSAIDs • Analgesic • Antipyretic • Anti-inflammatory	Aspirin (acetylsalicylic acid; ASA)	• Take with milk, food, or full glass of water • Avoid lying down for 15-30 minutes after ingestion • Do not use if a strong vinegar odor is present • Notify physician if tinnitus, shortness of breath, or bleeding occurs • Be aware of the potential for drug interactions and speak to a healthcare professional • Avoid use in children because of the relationship between viral illness, Reye's syndrome, and aspirin use • Avoid use if peptic ulcer disease is present
	Ibuprofen, ketoprofen, naproxen	• Take with milk, food, or full glass of water • Be aware of the potential for drowsiness or dizziness • Avoid use if peptic ulcer disease is present • Notify a physician in the event of weight gain, edema, rash, or bleeding because of the potential for GI intolerance, hematologic side effects, central nervous system side effects, and renal side effects • Half-lives vary, so products are not necessarily interchangeable

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
*Please see product labeling for each specific product for detailed information on use in pregnancy and breast-feeding, specific contraindications, and other usage information.

Other considerations included in product labeling are the use of medications during pregnancy or breast-feeding, and warnings to consult a physician if consuming 3 or more alcoholic drinks per day.

PAIN ACROSS THE LIFESPAN: MANAGEMENT IN COMMON CONDITIONS

Osteoarthritis

Goals of OA therapy are to relieve pain, minimize disability, and delay or prevent disease progression. Risk factors for OA include systemic variables such as female gender and increasing age, which increase susceptibility, and local biomechanical variables such as joint injury and obesity, which affect site and severity of OA.[60]

Optimal therapy for OA is multimodal and should be tailored to each individual. Numerous interventions have been studied. Consensus between the published guidelines is summarized in Table 3. Overall, good evidence shows that quadriceps strengthening can increase knee extension strength in both males and females.[61-63] Manual PT also increases strength as demonstrated on Western Ontario and McMaster Universities (WOMAC) scores.[64] Results of randomized controlled trials (RCTs) suggest that PT diminishes pain by 8% to 56%.[63-66]

Analgesia is a cornerstone of multimodal therapy. The American College of Rheumatology (ACR) recommends acetaminophen as first-line therapy for OA, which is an important issue for patient counseling.[67] Other available agents are nonselective and cyclooxygenase (COX)-2–selective NSAIDs, centrally acting analgesic agents, and adjuvants such as tricyclic antidepressants (TCAs) and muscle relaxants. When the maximum recommended dose of acetaminophen (4 g/d) does not provide adequate analgesia, analgesic doses of NSAIDs, or if necessary, anti-inflammatory doses, should be tried.[67] The prescription COX-2 inhibitor rofecoxib may offer greater therapeutic benefit in comparison to both celecoxib and acetaminophen.[68] Overall, however, acetaminophen and NSAIDs (selective and nonselective) appear to be equally efficacious (Table 4).[69,70] As always, benefits of therapy must be carefully compared to the inherent risks.

For other modalities, evidence is less consistent. Strong efficacy evidence in favor of sodium hyaluronate injections is lacking. Two of 3 large RCTs failed to demonstrate clear-cut benefits compared to placebo.[71-74] For arthroscopy, a 2-year study showed no differences among debridement, lavage, or placebo.[75] Glucosamine and chondroitin are widely utilized for treating OA. Efficacy data are mixed, and results of carefully designed studies are pending. Intriguingly, data supporting that glucosamine may delay disease progression in knee joints have been reported.[76,77]

In summary, current evidence on the management of OA supports the utility of systemic pharmacotherapy, selected use of topical pharmacotherapy,

TABLE 3

Management of OA: EULAR and ACR Consensus[166]

Nonpharmacologic Therapy	Pharmacotherapy	Surgery
• Patient education	• Acetaminophen	• Arthroplasty
• Personalized social support	• NSAID	
• Weight loss	• IA corticosteroid	
• Aerobic exercise	• Topical NSAID	
• Muscle strengthening	• IA hyaluronate	
• Range of motion exercises		
• Walking aids		
• Insoles		

OA, osteoarthritis; EULAR, European League Against Rheumatism; ACR, American College of Rheumatology; NSAID, nonsteroidal anti-inflammatory drug; IA, Intra-articular.

TABLE 4

A Comparison of Analgesics Used in OA*

	Efficacy	Dyspepsia	Serious GI Toxicity	Renal Toxicity	Cost
Acetaminophen	+ +	-	-	+ / -	+
OTC NSAID	+ +	+ + +	+ +	+ +	+ +
NSAID	+ +	+ + +	+ + +	+ +	+ + +
COX-2 Inhibitor	+ +	+ + +	-	+ +	+ + + +

- Acetaminophen for those with previous benefit, no prior use, mild disease, or high GI/renal toxicity risk
- NSAID for acetaminophen nonresponders, inflammatory component, severe disease
- COX-2–selective agent for acetaminophen nonresponders with high risk for a GI bleed

OA, osteoarthritis; GI, gastrointestinal; OTC, over-the-counter; NSAID, nonsteroidal anti-inflammatory drug; COX-2, cyclooxygenase-2.

* D.O. Clegg, MD, personal communication.

nonpharmacotherapy such as weight loss, exercise, patient education and behavioral programs, and joint replacement when needed.

Dysmenorrhea

Primary dysmenorrhea is painful menstruation in the absence of pelvic pathology. Resulting from endometrial release of prostaglandins ($F_{2\alpha}$ and E_2) during menses and from vasopressin activity, it can affect a large number of young women—up to 90%.[78-80] Treatment for primary dysmenorrhea is primarily pathology-directed.

Oral contraceptives reduce prostaglandin release and spontaneous uterine activity and are effective in ameliorating dysmenorrhea.[78,81] Nonselective NSAIDs, which inhibit prostaglandin synthetase, have been shown to provide relief in the majority of patients. In one study, 72% of patients experienced relief as compared to 15% with placebo treatment.[82] Relief has been reported in up to 90% of patients.[83] The more selective COX-2 inhibitors may also provide effective analgesia in dysmenorrhea. For example, valdecoxib was shown to have efficacy comparable to naproxen and superior to placebo.[84]

Calcium channel blockers such as nifedipine and verapamil can also reduce uterine motility and reduce pain, but are not generally considered good choices for young women because of their other effects.[85] Alternative approaches to treating primary dysmenorrhea include TENS, acupuncture, and topical heat, all of which have demonstrated some utility.[86-90] Surgical procedures are a last resort in primary dysmenorrhea.

Headache—A Focus on Migraine

Improved understanding of migraine pathogenesis and pain mechanisms has changed headache management strategies substantially. Once thought to be a vascular headache, migraine is now understood to be a neurovascular disorder. Research results indicate that genetic susceptibility, neuronal hyperexcitability, and cortical, trigeminal, and periaqueductal participation contribute to the pathogenesis of migraine headaches.[91,92] Given its substantially greater prevalence in women, migraine may also be influenced by gender differences in developmental and hormonal variables. For instance, menstrual migraine is one well-recognized migraine subtype.

Migraine presents with a spectrum of symptoms ranging from mild to severe and not necessarily according to the classic picture.[93] Even a stable pattern of primary headache may represent a form of migraine. Not only is migraine more common than previously realized, but a significant proportion of migraineurs—perhaps 40%—fail to receive a diagnosis.[94] Diagnosis has been aided by evolving criteria established by the International Headache Society (IHS).

The US Headache Consortium Guidelines are helping to provide a unified, evidence-based approach to evaluation and treatment of migraine.[95] Management involves accurate diagnosis, assessment of disability and comorbidities, patient education and participation, and pharmacologic treatment. Pharmacologic treatments encompass acute and preventive approaches. Some of the most effective medications are pathology-directed (for example, triptans in acute treatment and anticonvulsant agents in prevention). Acute management is intended to treat attacks and restore function.

Goals of prevention are to reduce migraine frequency, duration, and severity, improve or restore responsivity to acute treatment, increase function, and diminish disability. Acute therapies have been grouped with respect to evidence-based degree of benefit (Table 5). Preventive medications are classified into 5 categories (Table 6, page 6).

Patients who suffer with migraines should be educated that nonpharmacologic or combination modalities also play a role in reducing disability. Relaxation training, biofeedback techniques, and cognitive behavioral therapy are considered effective (Grade A; based on multiple well-designed trials, consistent findings). Behavioral therapy combined with preventive medications may also be efficacious (Grade B; some evidence from RCTs, but scientific support not optimal). Consensus (Grade C; the US Headache Consortium reached consensus on the recommendation in the absence of relevant RCTs) suggests that acupuncture, TENS, cervical manipulation, hypnosis, and hyperbaric treatments also afford some benefit.[96]

TABLE 5

Evidence Basis for Acute Therapies in Migraine Treatment

Clear Benefit	Moderate Benefit	No/Unknown Benefit
Over-the-counter	Opioids	Benefit not established
• Aspirin	• Acetaminophen, codeine	• Butalbital, aspirin, caffeine
• Aspirin, caffeine	• Meperidine	• Ergotamine with or as without caffeine (PO)*
• Acetaminophen, aspirin, caffeine	• Methadone	• Metoclopramide (IM, PR)
	• Butalbital, aspirin, caffeine, codeine	Clinically ineffective
Nonspecific	Other	• Acetaminophen
• Ibuprofen	• Butorphanol (IM)	• Chlorpromazine (IM)
• Naproxen	• Chlorpromazine (IM, IV)	• Lidocaine (IV)
• Butorphanol (IN)	• Isometheptene	
• Prochlorperazine (IV)	• Ketorolac	
	• Ergotamine plus caffeine*	Unknown benefit
Migraine specific	• Metoclopramide, (IV)	• Dexamethasone (IV)
• Sumatriptan (SC, IN, PO)	• Naproxen (PO)	• Hydrocortisone (IV)
• Zolmitriptan	• Prochlorperazine (IM, PR)	
• Rizatriptan	• Lidocaine (IN)	
• Naratriptan		
• Almotriptan		
• Frovatriptan		
• Eletriptan		
• Dihydroergotamine, (SC, IM, IN, IV)		

* Efficacy trials comparing ergotamine with placebo had mixed results. Strongest evidence for ergotamine efficacy was found in trials combining ergotamine with caffeine.

IN, intranasal; IV, intravenous; SC, subcutaneous; PO, orally; IM, intramuscular; PR, rectal.

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TABLE 6

Preventive Medications in Migraine Management

Group 1 Clear Evidence	Group 2 Moderate Evidence	Group 3 Consensus; No Evidence	Group 4 Efficacy, but Side Effects	Group 5 Evidence, No Efficacy
Amitriptyline	Aspirin	Cyproheptadine	Methysergide	Carbamazepine
Timolol	Atenolol	Bupropion	Flunarizine	Clomipramine
Divalproex sodium	Feverfew	Diltiazem	Pizotifen	Clonazepam
Propranolol	Fluoxetine	Doxepin		Indomethacin
	Gabapentin	Fluvoxamine		Lamotrigine
	Ketoprofen	Ibuprofen		Nicardipine
	Magnesium	Imipramine		Nifedipine
	Metoprolol	Methylergonovine		Pindolol
	Nadolol	Nortriptyline		
	Naproxen	Paroxetine		
	Nimodipine	Phenelzine		
	Verapamil	Protriptyline		
	Vitamin B2	Sertraline		
		Tiagabine		
		Topiramate		
		Trazodone		
		Venlafaxine		

Adapted with permission from Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55:754-762.

Acute and Chronic Low Back Pain

The differential diagnosis of low back pain should include nonspecific pain, nerve root pain, or possible serious spine pathology such as tumor or infection. Low back pain is typically classified according to its duration, ie, acute or chronic. Acute pain (less than 3 month duration) is usually mechanical and self-limiting, with 60% to 70% of back pain resolving within 6 weeks, and 80% to 90% by week 12.[97] Chronic pain, however, is more difficult to treat and recovery after 12 weeks is less certain—fewer than half of those individuals disabled for longer than 6 months return to work.[97] Pharmacologic and nonpharmacologic treatment of low back pain should aim at early intervention and symptom control in order to improve function and reduce pain.

Pharmacologic options are similar for both acute and chronic back pain: acetaminophen, NSAIDs/COX-2 inhibitors, muscle relaxants, acetaminophen combination products, and opioids. In addition, chronic back pain has been treated with TCAs.[98,99] In acute back pain, acetaminophen is effective in a variety of mild-to-moderate pain states and is well tolerated at recommended dosages.[100,101] NSAIDs are considered effective for short-term global improvement, but evidence is lacking for long-term therapy.[102]

In a meta-analysis,[103] NSAIDs were found to be more effective than placebo for acute back pain. Efficacy studies comparing NSAIDs with acetaminophen revealed conflicting results as no differences were found more often than not. NSAIDs may not be more effective than other drugs for acute low back pain, and differences among NSAIDs have not been demonstrated. In addition, NSAIDs have also not been proven more effective than physiotherapy or spinal manipulation.[103] In the primary care setting, muscle relaxants are used frequently in combination with NSAIDs for acute back pain. In a longitudinal study of 219 patients, those who received combinations of NSAIDs and muscle relaxants reported the best outcomes at a 1-week follow-up.[104]

For chronic back pain, opioids may provide significantly better results than an NSAID. In a small RCT comparing naproxen to either oxycodone or oxycodone plus sustained release morphine, patients experienced significantly less pain with the opioid treatments compared to naproxen. No significant abuse potential was observed, but benefits disappeared when doses were tapered.[105] Antidepressants also have some utility in chronic back pain in patients without depression, but the effect may be modest.[98] Injection therapy for chronic back pain is medically accepted, but definitive evidence of benefit is lacking.[106]

Recommended nonpharmacologic treatments for acute back pain include patient education, range of motion exercises, and spinal manipulation within the first month of symptoms.[107] Evidence is insufficient to support the use of traction, thermotherapy, ultrasound cutaneous laser treatment, TENS, biofeedback techniques, and back school. Prolonged bed rest is not recommended, as bed rest for more than 4 days may lead to debilitation.[107,108] For chronic pain, patient education, therapeutic exercise, and manipulation have demonstrated efficacy, but evidence does not support the use of traction, ultrasound, TENS, or electromyographic biofeedback.[108-110] Data are insufficient to support the use of thermotherapy, massage, electrical stimulation, and back schools in the treatment of chronic pain.[108,110]

Analgesics in Musculoskeletal Injuries: A Reassessment of the Issues

Soft tissue injuries occur in a number of conditions: sprains, strains, fractures, musculoskeletal overuse, and chronic tendon lesions. Despite obvious differences in these conditions, processes such as injury, inflammation, and healing are common to all. Even in fractures, soft tissue injury is a major component contributing to pain. Historically, anti-inflammatory analgesics have been used to treat these types of injuries. Accumulating evidence, however, suggests that this practice may need to be reconsidered.

In musculoskeletal injury, inflammation is an integral part of the healing process, which occurs in 3 phases: inflammatory, proliferative, and maturation. Each successive step depends on the previous one.[111,112] In tendinitis, more properly called tendinopathy or tendon lesion, no inflammation actually occurs, so blocking inflammation is unlikely to be beneficial.[113,114] As researchers gain more information on the physiology of injury and repair, treatment strategies will evolve to incorporate this knowledge. For example, in soft tissue injury in general, PT, in contrast to rest, may increase inflammation, decrease degeneration, and improve outcome.[115,116]

Delayed Onset Muscle Soreness. Both acetaminophen and NSAIDs are effective. No benefit of NSAIDs over acetaminophen has been demonstrated. Compared to placebo, NSAIDs have unequivocal analgesic properties, but do not result in improvements in muscle strength or alter release of creatine phosphokinase.[111] Data from animal studies suggest that NSAIDs may actually impair muscle healing, but no data in humans are available.[111] Therefore the benefits of NSAIDs are likely due to their analgesic but not anti-inflammatory properties.

Tendinitis. Because this process does not involve inflammation, beneficial effects of NSAIDs are probably limited to their analgesic properties.[114]

Sprains and Strains. The traditional and logical approach of rest, ice, compression, and elevation (RICE), has not been examined rigorously in clinical trials. Extended rest, however, may be detrimental to healing.[112] No placebo-controlled trials of acetaminophen have been reported in sprains. NSAIDs have been reported to be efficacious in some trials. In 6 of 15 trials reviewed, no differences compared to placebo were observed.[117] In addition, one study in rats indicated that the COX-2 inhibitor celecoxib may retard ligament healing.[118] For muscle strains, acetaminophen and NSAIDs produce similar effects in an animal model, but clinical data are lacking.[119]

Fractures. Bone and soft tissue injury are associated; moderate-to-severe pain derives from tissue trauma and inflammation. The enzyme COX controls bone healing and callus formation. Therefore any NSAID may impair bone healing, as demonstrated in animal and in vitro studies.[120] Whether these effects also occur clinically is unknown. Immobilization is critical in fractures, and pain may be ameliorated by surgery. Opioids and opioid combinations are useful initially. The efficacy of acetaminophen in pain management for acute fracture is undocumented.

In summary, the principles of managing musculoskeletal injury are to make an accurate diagnosis, separate the underlying problem from the pain, and treat each within the context of potential treatment side effects and impact on healing.

PAIN AND ANALGESIA: SPECIAL CONSIDERATIONS

Some subgroups of patients present special challenges in the management of their pain. For example, special considerations may be necessary in elderly patients and those with GI bleeding, liver disease, and/or cardiorenal disease.

The Elderly

Pain is ubiquitous in elderly patients, and is both a cause and result of medical conditions in this population. Thus, a multidisciplinary approach is needed. The results of 2 RCTs demonstrated that disease and pain management could be improved by specific interventions in the long-term care and outpatient settings. The results suggest that better overall care of older patients requires improved recognition and management of pain.[121-123]

Falls in Long-term Care Facilities. Falls create a substantial burden for patients and for facilities, including excess medical treatment, surgery, and deaths. Risk factors include both endogenous (functional impairment) and exogenous factors (eg, environmental hazards, drug use). Pain also can contribute to the falls, for example by increasing instability. In facilities in which consultation was undertaken to assess and alter environmental and personal safety, recurrent falls were reduced significantly.[122]

Reducing the Use of NSAIDs for OA in the Community Setting. Although NSAIDs are not first-line agents for OA because of the increased risks of GI and other potential complications, they are prescribed frequently for this condition in patients aged 65 years or older.[123] Researchers developed a program to educate community physicians about the ACR guidelines recommending acetaminophen as well as other interventions as preferred therapy. Modest reductions in NSAID use were found. No concomitant increases in the use of unsuitable medications were observed and musculoskeletal symptoms did not worsen.[123] More dramatic effects were observed when the study was conducted in the long-term care setting. Despite a significant decline in NSAID use and an increase in acetaminophen use in the homes receiving the educational interventions, no between-group differences were found in worsening of pain symptoms.[124]

Patients With Gastrointestinal Bleeding

Among analgesics used commonly for mild-to-moderate pain, NSAIDs as a class are associated with GI bleeding, which is related to COX inhibition and reduction of gastroprotective prostaglandins, direct deleterious effects on the gastric mucosa, and the inhibition of platelet aggregation.[125] NSAIDs include nonsalicylates (eg, ibuprofen, diclofenac), salicylates (eg, aspirin), and COX-2 inhibitors (eg, celecoxib). These agents do not carry equal degrees of risk. The prescription COX-2 inhibitors have improved GI safety profiles, thought to result from their more selective effects, but also are more expensive than traditional NSAIDs and acetaminophen.[126,127]

Risk factors for GI bleeding include history of prior bleeding, age, anticoagulant use, corticosteroid use, and NSAID dose.[128,129] The estimated risk of GI bleeding with various analgesics is shown in Table 7.[130] Based on a wealth of data, it is clear that NSAIDs, including OTC agents, are associated with both upper and lower GI risks. Aspirin contributes substantially to the risk, even when it is used occasionally or at low doses.[131-133] In a cohort study, the risk of GI bleeding in a population taking low doses (100 mg -150 mg once daily) of aspirin was increased over the general population by a factor of 2.6 (95% confidence interval [CI]: 2.2-2.9). For low-dose aspirin combined with NSAIDs, the risk was increased 5.6 fold (95% CI: 4.4-7.0).[134] The Celecoxib Long-term Arthritis Safety Study (CLASS) demonstrated that celecoxib was associated with a lower incidence of combined upper GI ulcer complications and symptomatic ulcers than ibuprofen and diclofenac, but the rates of these complications were highest in patients who were also taking aspirin.[135] The use of aspirin also negated the difference between celecoxib and the comparator agents.

Based on an assessment of a large body of clinical evidence, it was concluded that the rank order of GI safety for analgesics (safest to least safe) is acetaminophen, COX-2 inhibitors, dual COX-1 and COX-2 inhibitors, and aspirin. Enteric coating and buffering do not reduce risks associated with aspirin.[133,134] These effects are important because of the widespread use of these agents and because of the increased risk when combinations are used.

Analgesic Use and Liver Function

The use of analgesics in patients with liver disease or those who use more than a moderate amount of alcohol regularly is a subject of some controversy and ongoing investigation. Acetaminophen is used frequently to treat mild-to-moderate pain in patients with liver disease because they are at risk for upper GI hemorrhage. Metabolized primarily in the liver by glucuronidation, sulfation, and oxidation, a large overdose of acetaminophen can lead to hepatotoxicity in patients without liver disease, primarily because of oxidative metabolites. It has been speculated that patients with compromised liver function—for example, those with a history of liver disease or alcohol abuse—may be at increased risk when using acetaminophen. The data, however, do not appear to support this hypothesis.

In patients without liver disease, acetaminophen is metabolized primarily by glucuronidation and sulfation. A small portion, perhaps 5%, is converted to a reactive metabolite that can injure the liver cell. This metabolite is normally detoxified by glutathione. Chronic liver disease does not cause glutathione deficiency nor does it shift metabolism to the oxidative

TABLE 7

GI Bleeding Associated With Analgesics

Analgesic	Case, % (n=627)	Control, % (n=590)	OR	95% CI
OTC use of				
Aspirin	27.0	12.0	2.7	1.9-3.8
Ibuprofen	10.1	5.8	2.4	1.5-3.9
Acetaminophen	4.5	6.3	0.9	0.5-1.6
Total OTC NSAIDs	36.2	17.5	3.0	2.2-4.1
Rx NSAIDs	9.3	5.9	2.1	1.2-3.4
Total NSAIDs	42.9	22.0	3.1	2.3-4.1

GI, gastrointestinal; OR, odds ratio; CI, confidence interval; OTC, over-the-counter; NSAID, nonsteroidal anti-inflammatory drug; Rx, prescription.

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pathway.[136,137] Furthermore, no accumulation of acetaminophen has been found in patients with cirrhosis of the liver, despite a slightly increased half-life.[138] Acetaminophen given at 4 g/day has been shown to be well tolerated in patients with stable chronic liver disease. It does not appear to affect alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, nor does it accumulate in serum or tissues beyond normal levels.[139,140] Despite these findings, a recent survey showed that 95% of PCPs and 80% of gastroenterologists (GEs) consider cirrhosis a risk factor for acetaminophen hepatotoxicity.[141] Thus, only 38% of PCPs and 66% of GEs considered acetaminophen preferable to NSAIDs in patients with cirrhosis.

It is widely recognized that excess alcohol use increases bleeding risks associated with salicylates and other NSAIDs, but published data on the safety of acetaminophen in recommended doses and the risk of increased hepatotoxicity are conflicting. A recently published systematic review by Dart and colleagues identified articles that pertained to the use of recommended doses (≤4 g/d) of acetaminophen by adult patients with alcoholism.[142] Two Class I studies (blinded RCTs), 5 Class II studies (prospective, nonrandomized, or nonblinded clinical trials, cohort or well-designed case-control studies, dramatic results in uncontrolled studies and volunteer studies), and 25 patients in 20 Class III studies (retrospective case series, case reports) were included.[142]

Class I and II data demonstrate little, if any, risk of liver injury in alcoholic patients that ingest a therapeutic dose (≤4 g/day) of acetaminophen. Only Class III data describe an association of therapeutic acetaminophen ingestion with liver injury in patients with alcoholism.[142] The retrospective data of Class III studies, however, are usually incomplete and occasionally conflicting. Inaccuracies in the patient's history are probable, especially regarding dose of acetaminophen ingested. Relevant data are summarized below.

Class I Data. Patients (N=201) entering an alcohol detoxification program were randomly assigned to receive 4 g/day acetaminophen or placebo for 2 consecutive days.[143] No statistically significant differences in ALT and AST levels between acetaminophen- or placebo-treated patients were detected.

Class III Data. Over 40 case reports of more than 49 patients were reviewed. The patients had histories of severe alcoholism as well as other medical problems including other causes of liver damage. In a typical example, a 67-year-old male who was an occasional drinker ingested acetaminophen at a dose of 1 to 3 g/day for 3 days.[144] His level of acetaminophen was 27.5 µg/mL 72 hours after his last dose. Serum AST was 3125 U/L. He experienced acute renal failure during the episode and had a history of heart disease, lung disease, chronic hypoxia, status post–coronary artery bypass, vagotomy, and pyloroplasty. Serology tests for infection were negative, and the biopsy showed centrilobular necrosis, which is consistent with acetaminophen toxicity. The interpretation of this case is difficult because 3 days after his last dose of acetaminophen, blood levels were still equal to the entire amount of acetaminophen reported to have been ingested over 3 days. In another example, a 56-year-old male who admitted to drinking one-half bottle of brandy per day ingested 2.4 to 3.2 g/day of acetaminophen.[145] A biopsy showed centrilobular necrosis. Again, interpretation is difficult because a history of alcohol abuse is likely to impair the accuracy of memory. In neither of the cases were other causes of centrilobular necrosis adequately excluded.

In summary, the findings of prospective studies suggest that recommended doses of acetaminophen can be used safely in patients with mild-to-moderate pain and possible liver disease or impairments due to alcohol abuse. Doses above 4 g/day have not been studied, and patients should be cautioned not to exceed the recommended dose. It should also be noted that the product labeling for all OTC analgesics contains the following warning: "If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [analgesic] or other pain relievers/fever reducers."[146]

Patients With Cardiorenal Disease

Four important questions relate to the use of common analgesics and potential cardiovascular and renal effects:

1. Do commonly used analgesics cause chronic renal failure? The association between lifetime cumulative use of various analgesics and end stage renal disease (ESRD) has been examined in a case control study.[147] When the odds ratio (OR) for lifetime acetaminophen use of 0 to 999 pills was set to 1.0, the OR for a usage of 1000 to 4999 was 1.1 (95% CI: 0.7-1.6). For a lifetime usage of over 5000 pills, the OR was 1.6 (95% CI: 0.9-2.9). Aspirin use was associated with a decreased OR for ESRD of 0.7 (95% CI: 0.5-0.9) when the cumulative usage was 1000-4999 pills. No increased risk was observed with higher usage. NSAIDs were associated with an increased OR of 4.5 (95% CI: 1.0-19.5) only at a cumulative usage of more than 5000 pills.

In contrast, a 14-year prospective study in a cohort of 11,032 male physicians assessed early renal failure as defined by creatinine levels of greater than 1.5 mg/dL and reduced creatinine clearance as estimated by glomerular filtration rates less than 55 mL/min/1.73 m^2. Use of acetaminophen, aspirin, and other NSAIDs was assessed by self-report.[148] The RR of elevated creatinine levels was 1.0 for no use of any analgesic. For acetaminophen, RRs and 95% CIs, ranged from 0.74 (0.58-0.94), for 12 to 1499 pills to 0.81 (0.50-1.31) for 2500 pills or more. The reduction in the RR from no use was statistically significant (P=.04), but the absolute differences in creatinine levels were small. Neither aspirin nor NSAIDs were associated with an increased RR of renal dysfunction.

2. Do commonly used analgesics cause hypertension? The Nurses' Health Study examined the association of acetaminophen, aspirin, and NSAID use with self-reported, physician-diagnosed hypertension in a prospective cohort of 80,020 participants.[149] Both NSAIDs and acetaminophen were associated with increased risks of hypertension. RRs increased as analgesic use increased. In the highest use category (≥22 days/month) NSAID use was associated with an RR for hypertension of 2.69 (95% CI: 2.22-3.26). Similar associations occurred with acetaminophen use (RR: 2.83; 95% CI: 2.20-3.65). Aspirin use was not associated with an increased RR. Preliminary results of the Physicians' Health Study (PHS), however, suggest that these associations may disappear when adjustments for obesity and other risk factors are made.[150]

3. Can analgesics cause salt and fluid retention and increased blood pressure in susceptible patients? Hypertension and congestive heart failure are likely to coexist with arthritis and renal disease. The mechanisms of action of NSAIDs suggest that they could influence salt and water retention and hypertension.[151] Non-NSAID analgesics, such as acetaminophen, do not appear to have renal effects.[152,153] In meta-analyses, increases in blood pressure occurred in patients using NSAIDs with hypertension, including those on treatment.[154] In one analysis, indomethacin and naproxen were associated with the greatest increases in blood pressure.[155] A multicenter RCT indicated that both celecoxib and rofecoxib were associated with the development of edema and hypertension.[156]

Answer Key: 1 b; 2 a; 3 a; 4 b; 5 d; 6 a; 7 c; 8 d; 9 e; 10 a; 11 b; 12 c; 13 b; 14 a; 15 a.

4. Do NSAIDs interfere with the cardioprotective effects of aspirin? Some reports suggest that NSAIDs can negate the cardioprotective effects of aspirin. For example, individuals who received an ibuprofen prescription and were followed in a registry appeared to have an increased risk of cardiovascular and all cause mortality, but this was not a controlled study.[157] In the randomized PHS, based on self-reported NSAID use, the analysis suggested that regular use of NSAIDs interfered with the cardioprotective benefits of aspirin on first myocardial infarction.[150] The interference could be the result of competitive interactions at the shared docking site on COX-1.[150] Additional studies are needed to determine effects in women and whether results differ according to the specific NSAID.

This discussion suggests that all analgesics should be used cautiously in patients with cardiorenal conditions. There is no evidence, however, that analgesic use causes renal disease in a healthy population. More research is needed to evaluate the risks associated with classes of analgesics and with individual agents in at-risk populations. Regarding the potential interference of NSAIDs with the cardioprotective effects of aspirin, some evidence supports such a possibility but larger, controlled studies are needed.

SUMMARY AND CONCLUSIONS

Pain is a multidimensional experience, the perception of which is influenced by numerous environmental and endogenous factors. Gender and ethnic differences in pain prevalence, pain thresholds, and responsivity to medications are significant. Major impediments to optimal pain management remain—these include recognition of the consequences of pain, lack of proper education, time and cost constraints, patients' needs and expectations, and attitudes of healthcare providers. Comprehensive pain management must incorporate the triad of psychosocial interventions, physical modalities, and pharmacotherapy. Moderate-to-strong evidence supports the utility of a number of psychosocial and physical interventions in pain management—education, self-efficacy, cognitive behavioral therapy, exercise, weight loss, relaxation, and stress management.

Pharmacotherapy is a cornerstone of pain management for both acute and chronic pain. For chronic pain, potential side effects of long-term therapy are a major consideration in the decision-making process. In some conditions, for example dysmenorrhea and migraine, treatment selection may be directed by the underlying pathophysiology. In musculoskeletal injuries, increased understanding of the physiology of healing and the positive role of inflammation is changing practice protocols from the standard use of NSAIDs to increasing use of acetaminophen, which lacks anti-inflammatory properties.

In many pain conditions, nonprescription agents can be integrated with other modalities and play a fundamental role in analgesia. The selection of a specific agent can depend on comorbid medical conditions and risk factors. Other than in pain states with known pathology-directed therapy (eg, dysmenorrhea), acetaminophen is probably the first-line therapy for mild-to-moderate pain based upon balancing safety, efficacy, and cost. In all cases, patient education is essential to emphasize that all medications, including those that are available OTC carry both risks and benefits, including the potential for drug-drug interactions. Unless consumers read the labels, they are at risk for ingesting excess amounts of certain medications contained in different formulations. PCPs, physician assistants, nurse practitioners, pharmacists, and other healthcare professionals can improve consumer use of OTC products by paying attention to factors influencing safe and effective use, by taking an adequate history that includes all medication usage, and by counseling their patients on specific issues.

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STATE-OF-THE-ART MANAGEMENT OF MILD-TO-MODERATE PAIN FROM ADOLESCENCE THROUGH OLD AGE PROCEEDINGS HIGHLIGHTS

Post-Program Self-Assessment/CME Verification

If you wish to receive CME credit and confirmation of your participation, please mail a photocopy of this completed form before May 30, 2005 to:

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Instructions:

For each of the questions or incomplete statements below, indicate the most appropriate response on the Registration/Evaluation Form below.

1. On the numerical and visual analog scales, mild-to-moderate pain is defined as a score of:
   a. 2-4 c. 3-5
   b. 2-6 d. 3-6

2. The International Association for the Study of Pain® defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage…"
   a. True b. False

3. Characteristics of pain perception include all except which one of the following?
   a. Gender differences, which emerge in humans at birth
   b. Ethnic differences
   c. Bidirectional effects of stress

4. Approximately what percentage of adults in the United States visit a doctor only when their pain becomes intolerable?
   a. 89% c. 42%
   b. 64% d. 26%

5. Which of the following statements is/are true?
   a. One-third of healthcare expenditures associated with arthritis management results from GI adverse effects.
   b. Patients with musculoskeletal conditions are 50% more likely to utilize healthcare services than those without such chronic conditions.
   c. Physicians treating patients in pain are more likely to spend time on technical behaviors than on preventive services.
   d. All of the above
   e. None of the above

6. There is strong evidence that relaxation techniques can reduce pain.
   a. True b. False

7. Among OTC pain medications, which one of the following statements is true
   a. Combination products typically provide enhanced pain relief.
   b. Combination products should be tried first.
   c. Combination products have a greater potential for side effects.
   d. Combination products have an improved benefit-to-risk ratio over single agents.

8. In the context of multimodal interventions for OA, recommended first-line pharmacologic therapy is:
   a. Aspirin c. Nonselective NSAIDs
   b. COX-2 inhibitors d. Acetaminophen

9. For dysmenorrhea, first-line therapy is considered to be:
   a. Calcium channel blockers
   b. NSAIDs
   c. Oral contraceptives
   d. a and c
   e. b and c

10. Treatment of migraine is directed toward the underlying pathology, which is understood to be:
    a. Neurovascular c. Vascular
    b. Stress-induced d. Neuropathic

11. In acute lower back pain, recommended nonpharmacologic treatments include:
    a. Bed rest and traction
    b. TENS and thermal therapy
    c. Both a and b
    d. Neither a nor b

12. In soft tissue injury:
    a. Physical therapy is undesirable
    b. Inflammation should be minimized
    c. Rehabilitation plus simple analgesics should be used
    d. Extended rest is recommended

13. The rank order for GI safety of analgesics is:
    a. COX-2 inhibitors, acetaminophen, nonselective NSAIDs, aspirin
    b. Acetaminophen, COX-2 inhibitors, nonselective NSAIDs, aspirin
    c. Acetaminophen, COX-2 inhibitors, aspirin, nonselective NSAIDs
    d. COX-2 inhibitors, acetaminophen, aspirin, nonselective NSAIDs

14. At doses of ≤4 g/day, acetaminophen has not been shown to increase the risk of bleeding in patients with chronic liver disease or a history of alcohol intake.
    a. True b. False

15. Which of the following statements is false?
    a. Evidence-based analyses indicate that all analgesics can cause renal disease in a healthy population.
    b. Some evidence supports the view that NSAIDs can interfere with the cardioprotective effects of aspirin.
    c. Analgesic effects on hypertension may be associated with other risk factors such as obesity.
    d. Aspirin has not been associated with increased hypertension.

Please see page 8 for the Answer Key. Please record your posttest answers: 1.____ 2.____ 3.____ 4.____ 5.____ 6.____ 7.____ 8.____ 9.____ 10.____ 11.____ 12.____ 13.____ 14.____ 15.____

Registration/Evaluation

The University of Colorado School of Medicine would appreciate your comments regarding the quality of the information presented, and thanks you for your participation.

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. The program objectives were fully met.	a	b	c	d
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.	a	b	c	d
3. The educational activity has enhanced my professional effectiveness and improved my ability to:				
A. Treat/manage patients	a	b	c	d
B. Communicate with patients	a	b	c	d
C. Manage my medical practice	a	b	c	d
4. The information presented was without promotional or commercial bias.	a	b	c	d
5. The program level was appropriate.	a	b	c	d

6. Suggestions regarding this material, or recommendations for future presentations:

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